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TITLE: A Phase II Immunotherapeutic Trial: Combination Androgen Ablative Therapy and CTLA-4 Blockade as a Treatment for Advanced Prostate Cancer

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14. ABSTRACT

The objectives of this study are to generally test whether the addition of CTLA-4 blockade can enhance clinical treatment responses in advanced prostate cancer patients compared with treatment with AA therapy alone. Patients will be randomized to 3 months of concurrent AA therapy + MDX-010 or 3 months of initial AA therapy alone. Of 25 enrolled patients, approximately 10 have received sufficient follow-up to assess whether any treatment effects may be occurring: 10 patients have received AA therapy alone; 11 patients have received AA therapy + MDX-010. Those 11 patients who have received AA therapy alone. Specifically, the 11 test subjects have experienced faster declines in PSA, suggesting that MDX-010causes hormone therapy to work more effectively than using hormone therapy alone. We have observed that some of the test subjects experienced a more prolonged response (diminished PSA) relative to those that received hormone therapy alone. Based on these preliminary observations, our strong hunch is that patients who received AA therapy + MDX-010 treatment may be deriving a benefit from the experimental form of therapy beyond that which occurs using standard treatment (which is hormone therapy alone).

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Introduction

This is an open-label randomized phase II trial in which 108 patients with advanced prostate cancer will be prospectively enrolled onto study. Upon enrollment patients will be immediately randomized to receive either: i) 3 months of concurrent AA therapy + MDX-010 (treatment group) or ii) 3 months of initial AA therapy alone (control group). Equal numbers of control and treatment group patients will be enrolled onto study.

Body

Since the time of our last report, we have enrolled 14 additional participants on this protocol at Mayo Clinic Rochester and have considered an additional 28 potential participants who were deemed ineligible.

This brings our total study enrollment to 25 with a total of 50 potential participants considered but deemed ineligible.

We feel that the previous eligibility criteria were too narrow and limited our enrollment. Approximately 50 percent of the referrals that we received were patients who had recently been started on hormone therapy. Significant numbers were also excluded due to the "limited metastases" inclusion criteria. Therefore, we are broadening the eligibility criteria to facilitate accrual without compromising the interpretation of outcome data pertaining to the treatment of patients with local or advanced prostate cancer receiving treatment on the study. In addition, we anticipated that the UCSF site would enroll 54 participants, however they were unable to screen or enroll any participants on this trial and are therefore being removed as a study site.

A protocol revision dated August 28, 2006, was submitted to the Department of Defense on August 31, 2006. Protocol revisions consisted primarily of expanding the inclusion criteria to include patients with any T stage prostate cancer, with or without metastatic disease (with the exclusion of central nervous system metastases), staged within 180 days of enrollment, including post-prostatectomy patients with a rising PSA and including patients who have initiated hormone therapy $\leq$21 days prior to enrollment. Protocol revisions also included removing the University of California, San Francisco as a study site since they have been unable to screen or enroll any participants.

These protocol and consent form revisions were approved by the Department of Defense Human Subjects Research Review Board on December 20, 2006, and by the Mayo Cancer Center RAS Committee on December 20, 2006; these revisions have now been submitted to the Mayo IRB.

We continue to aggressively work to accrue study participants, continue to maintain good working relationships with the staff urologists, residents, and PAs in the Department of Urology, and plan to continue with the previously established recruitment activities. These activities have consisted of:

- distributing printed flyers to staff urologists, residents, and physician assistants (PAs)
- posting study flyers on intra-clinic bulletin boards
- posting study flyers in all of the exam rooms

- sending weekly e-mail notifications to staff physicians, residents, and PAs
- scheduling individual one-on-one meetings with Dr. Kwon and the staff urologists
- presentations of the protocol at staff and resident meetings
- daily review of physician calendars for potential participants
- daily telephone calls to physicians, residents, and PAs each morning asking for referrals of any potential participants that they may see during the day
- networking with nurses, technicians, paramedical personnel, appointment schedulers, and other RN study coordinators within the Department of Urology

In addition, the RN coordinator recently presented this protocol to the Department of Urology as part of the monthly Urology Education Series.

Once the recent protocol revisions are approved by the IRB, we anticipate that enrollment will increase significantly. A major factor currently excluding potential participants is that many new prostate cancer patients receive an injection of Lupron from their local urologist within a week or two prior to coming to Mayo for a second opinion. By expanding our eligibility criteria to allow for these participants who have initiated hormone therapy $\leq$21 days prior to enrollment, many of the referrals that we receive from the clinical practice will now be eligible for enrollment. In addition, the inclusion of patients with any T stage prostate cancer, with or without metastatic disease, including post-prostatectomy patients with a rising PSA, should also greatly facilitate enrollment. We are confident that adequate progress can be made in the accrual to our trial.

At Mayo Clinic Rochester we have enrolled 25 advanced prostate cancer patients in our study and have randomized 21. Of these patients, roughly 10 have sufficient follow-up to assess whether any treatment effects may be occurring: 10 patients are regarded as "control" patients and have only received hormone therapy (removal of testosterone only, which is considered standard of care); 11 patients are considered "test" subjects and have received hormone therapy in combination with MDX-010 (an immune-boosting experimental agent that has been shown to promote cancer regression).

Thus far, those 11 patients who have received the combination of hormone therapy along with MDX-010 have generally demonstrated greater responses than patients that have received only hormone therapy alone. Specifically, the 11 test subjects have experienced faster declines in their PSA (prostate specific antigen) which is a blood marker that correlates with the extent of prostate cancer within their body. This suggests that MDX-010 causes hormone therapy to work more effectively than using hormone therapy alone.

Additionally, we have observed that some of the test subjects experienced a more prolonged response (diminished PSA) relative to those that received hormone therapy alone. Based on these preliminary observations, our strong hunch is that patients who received hormone therapy plus MDX-010 treatment (immune boosting) may be deriving a benefit from the experimental form of therapy beyond that which occurs using standard treatment (which is hormone therapy alone).

Key Research Accomplishments

- Protocol amendment dated 8-28-06 approved by the DOD HSRRB and the Mayo Cancer Center; currently under review by the Mayo IRB.
- Twenty-five study participants enrolled.

Reportable Outcomes

No reportable outcomes have resulted from this research to date.

Conclusion

Thus far, we have enrolled 25 advanced prostate cancer patients in our study. Of these patients, roughly 10 have sufficient follow-up to assess whether any treatment effects may be occurring. Ten patients are regarded as "control" patients and have only received hormone therapy (removal of testosterone only, which is considered standard of care). Eleven patients are considered "test" subjects and have received hormone therapy in combination with MDX-010 (an immune boosting experimental agent that has been shown to promote cancer regression).

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Please see the attached table.

References

No publications have resulted from this research to date.

Appendices

Not applicable.

Supporting Data

See attached table.

Supporting Data – PSA Values

Obs	DCNTR_ID	psa1	psa2	psa3	psa4	psa5	psa6	psa7	psa8	psa9	psa10	psa11	psa12	psa13	psa14
1	1388600	39.40													
2	1541331	49.80	52.30	4.50	0.60	0.30	0.52	5.50	10.00	11.70	17.90	27.30	30.30		
3	1628071	88.80	73.30	19.50	13.40										
4	2115904	19.30	2.10	1.40	0.80	4.30	7.90	8.20	11.20	11.50	13.30				
5	2179235	9.40	7.50	0.73	0.10	0.10	0.12	2.50	4.50	5.10					
6	2981667	8.90	0.60	0.20	0.10										
7	3348686	41.00	43.30	20.50											
8	3386306	39.50	3.90	0.70	0.35	0.21	1.30	4.80	4.70						
9	3785205	73.10	82.50	7.50	1.60	0.80	0.60	9.60	13.10	16.60					
10	4455469	4.90	2.60	0.30	0.21										
11	4499281	0.50	0.10	0.10	0.80	1.40	1.60	2.10	2.10	2.70	2.50	3.20	2.90	2.80	3.60
12	5106034	8.80	6.60	3.30	3.30	1.90	0.97	0.34	0.10	0.10	0.10	0.10			
13	5141309	10.80	1.80	0.40	0.20	0.26	0.52	0.69	1.20	2.40	3.50	3.90	6.90	7.80	
14	5722261	31.60													
15	6267662	7.70	0.50	0.10	7.00	0.40	2.50	4.10	5.90	7.60	7.80	11.10	14.50		
16	6274363	97.30	48.80	57.00	54.60										
17	6277932	158.0	136.0	1.70	0.20	0.10	0.10	1.50	7.60	16.60					
18	6288194	19.60	1.50	0.10	0.10	0.10	1.30	4.40	5.90	6.50	6.80	7.80	8.10	7.50	10.30
19	6291185	10.00	6.90	0.30	0.10	0.10	1.50	3.30	5.30						
20	6299282	21.70	9.50	1.40	0.80	1.40	4.50	6.30	8.30	14.10	17.70	18.90			
21	6307324	6.90	7.20	8.40	0.80	0.14	0.10	0.89	2.10	3.50	5.00	4.90	6.40		
22	6342916	58.90	50.30	23.10	9.00	3.90	2.20	0.47	0.29	0.33	5.90				
23	6373347	1120													